AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figures 1-5. These sheets, which include Figures 1-5, replace the original sheets including Figures 1-5. In Figures 1-5, previously omitted designations (A, B, C, etc.) for each individual structure have been added. No new matter has been added.

Attachments: Replacement Sheets

REMARKS

Amendments to the Claims

New dependent claim 71 is added for oral administration. The claim is supported by claims 25, 35, 43 and 52. Claims 23, 34, 41, 42, 49 and 50 are amended to more accurately define the subject matter of the invention. No new matter has been introduced by the amendments, and their entry is respectfully requested. Upon entry of the present amendments, claims 23, 25-31 and 33-71 are pending in this application.

I. The Objection to the Drawings Should be Withdrawn.

On page 2 of the Office Action, the Examiner objects to the Drawings (Figures 1-5) because the drawings do not have designations for each individual structure within figures.

In response to the Examiner's objection, Applicant has amended the Drawings and provided designations (A, B, C, etc.) for each individual structure, and no new matter has been added. These amended Drawings are provided in the Replacement Sheets found in the Appendix to this response. Accordingly, Applicant respectfully requests that the objection to the drawings be withdrawn.

II. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn.

Claims 23, 25-31, and 33-58 remain rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over Sugiura, Mückter, or Mau'ad. (pages 3-6 of Office Action). Applicant respectfully traverses these rejections.

1. Sugiura teaches away from the present invention and fails to render the claims obvious.

The Examiner alleges the claimed invention to be unpatenable over Sugiura. (Office Action, pages 3). Applicant respectfully traverses the rejection.

Under current law, a prior art reference or references cannot render a claim obvious unless the PTO provides evidence that the reference or references meet a three-part test for *prima facie* obvious. To begin with, the prior art reference or references must provide "motivation, suggestion, or teaching of the desirability of making the specific combination

that was made by the applicant." *See In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 2005). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2d 1385, 1397 (Fed. Cir. 1999); *Princeton Biochemicals, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d at 1054; *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334, 63 U.S.P.Q.2d 1374, 1387 (Fed. Cir. 2002). Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); *Boehringer Ingelheim Vetmedica, Inc.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d 1961, 1971 (Fed. Cir. 2003); *Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1516 (Fed. Cir. 2004). Further, "[b]oth the suggestion and the reasonable expectation of success 'must be founded in the prior art, not in the applicant's disclosure.'" *Noelle*, 355 F.3d at 1352, 69 U.S.P.Q.2d at 1515-16 (quoting *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1569, 39 U.S.P.Q.2d 1321, 1327 (Fed. Cir. 1996).

In the previous response, Applicant demonstrated that Sugiura lacks the legally required expectation of success, because Sugiura discloses that thalidomide has only a moderate inhibitory effect on Lewis bladder carcinoma in mice, rats and hamsters, despite repeated injections with significantly high doses of thalidomide of 1,000mg/kg/day, and has practically no inhibitory effect on the growth of 24 other mouse, rat and hamster tumors. Also, Applicant submitted that because the results of Sugiura are so poor and no significant degree of antineoplastic activity was demonstrated in animals, much less in humans, Sugiura fails to suggest the claimed invention to those of ordinary skill in the art.

Nevertheless, the Examiner alleges that "Sugiura nonetheless teaches the inhibition of growth of tumors sensitive to thalidomide, *i.e.*, inhibition of Lewis bladder carcinoma." (Office Action. page 3). Moreover, the Examiner alleges that "the effectiveness of thalidomide against other tumor types is not at issue in the instant claims." (Office Action, page 3) (emphasis added). However, Applicant respectfully submits that the reported "effectiveness" in the prior art is indeed relevant in determining whether the second prong of the three-part test for obviousness is met, that is, whether there is a reasonable expectation of success.

Sugiura discloses that thalidomide had practically no inhibitory effect on the growth of 24 mouse, rat and hamster tumors, but only a moderate inhibitory effect on a single tumor type Lewis bladder carcinoma, which effect was only seen after extremely high doses were administered to the animals -- 1,000mg/kg/day. Those skilled in the art would not be motivated by Sugiura even to try thalidomide in humans[1]. Indeed they would interpret Sugiura's as demonstrating that thalidomide would not be effective in inhibiting tumor formation or growth in humans. Therefore, the claims are not obvious in view of Sugiura.

Further, one of ordinary skill in the art would not have any expectation of successfully practicing the claimed invention in inhibiting the formation or growth of tumors in humans, much less at the doses of 0.1 to 300 mg/kg/day recited in claim 27 (where much lower dose than 1,000mg/kg/day is used) or in the cancer patients recited in claim 34. In fact, this interpretation is found in and evidenced by the peer-reviewed article Mückter which cites Sugiura's test results and describes that "in nearly all of the experiments, no indication of cytostatic action of thalidomide was observed." (Table 1, page 531 of Mückter). Again, this is actual evidence of what a person of ordinary skill in the art thought of teachings of Sugiura prior to the instant invention. In determining a *prima facie* case of obviousness, the Patent Office cannot ignore, and must consider what one of ordinary skill in the art would interpret the reference and all the evidence that an applicant submits. (Manual of Patent Examining Procedure § 2142).

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[1] At most, Sugiura provides a mere invitation to experiment on more animals with different cancers in the hope of obtaining better results. This "obvious to try" is not a legitimate test of obviousness. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988). *See also Novo Nordisk A/S v. Becton Dickinson and Co.*, 304 F.3d 1216, 1219 (Fed. Cir. 2002).

Further, Sugiura actually teaches away from the present invention. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference..." *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994) (emphasis added). "A reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Id.* (emphasis added). One of ordinary skill would be discouraged from Sugiura's poor result that 24 tumors did not respond to thalidomide and only moderate inhibitory effect was shown on a single Lewis bladder carcinoma with thalidomide repeatedly injected at the significantly high doses of 1,000mg/kg/day. Moreover, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Sugiura did not suggest any human trials or tests, much less the claimed invention. Also, one of ordinary skill in the art would not have been motivated to modify Sugiura in view of the poor results, as evidenced by Mückter.

Further, Applicant respectfully submits that the Examiner is improperly taking the Lewis bladder carcinoma result out of context. As the Examiner is well aware, a reference must be considered as a whole. See *e.g. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* 796 F.2d 443, 230 U.S.P.Q 416 (Fed. Cir. 1986), *cert. denied*, 484 U.S. 823 (1987) (A single portion in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness, but rather, a reference should be considered as a whole, and portions teaching away from the claimed invention must be considered). Sugiura discloses the inhibition of Lewis bladder carcinoma to be only moderate, if high doses of thalidomide are employed -- 1,000mg/kg/day. In addition, the lack of inhibitory effect in 24 other mouse, rat and hamster tumors must be considered. Therefore, Applicant respectfully submits that Sugiura, when considered as a whole, teaches away from the claimed invention.

In sum, the poor results in Sugiura as a whole fail to provide one skilled in the art a reasonable likelihood of success in practicing the claimed invention, and a *prima facie* case of obviousness has not been established. In fact, one reasonably skilled in the art would be discouraged from pursuing the present invention and Sugiura actually teaches away from the present invention. Applicant respectfully requests that the rejection over Sugiura be withdrawn.

2. Mückter also fails to render the claims obvious.

The Examiner alleges the claimed invention to be unpatenable over Mückter. (Office Action, pages 4).

In the previous response, Applicant submitted that Mückter cannot render the present invention obvious, because (1) in experiments on rats, thalidomide merely showed some responses in delaying the appearance and growth of tumors over a period of four to five weeks, but abated after about six weeks of treatment, when tumors grew again at rates comparable with those of controls; (2) the effect in rats is limited by the size of the tumor at the time of first administration and by the duration of treatment; and (3) in experiments on mice, thalidomide did not influence either the number or growth of tumors.

Nevertheless, the Examiner alleges that Mückter teaches the "treatment of DMBA tumors" because "thalidomide retarded in a most impressive fashion the manifestation and growth of tumors induced in rats by the carcinogen DMBA, even though the effect of thalidomide was limited by the size of the tumors at the time of first application, and by the duration of treatment." (Office Action, page 4, internal quotations omitted). Moreover, the Examiner alleges that "the effectiveness of the treatment is not at issue in the claims." (Office Action, page 4).

As stated above, Applicant once again respectfully submits that the reported "effectiveness" in the prior art is indeed relevant in determining whether the second prong of the three-part test for obviousness is met, that is, whether there is a reasonable expectation of success. Mückter discloses that thalidomide was ineffective in treating tumors in rats after six weeks and ineffective in treating tumors in mice. (Pages 536-537 and 537-538, respectively). This disclosure would not have provided one of ordinary skill in the art with a reasonable expectation of success in practicing the claimed methods even in animals, much less in humans as claimed. Mückter would not provide one of ordinary skill in the art with the impetus to pursue the present invention. Indeed, one of ordinary skill in the art would be discouraged from using thalidomide for the treatment of tumors in humans and would not find the present invention likely to be productive.

Further, in response to the argument that thalidomide was not effective in the mouse model of tumor growth in Mückter, the Examiner alleges that "one of ordinary skill in the art

would have given more weight to the guidance of the rat models" because "Sprague Dawley rats are considered relevant animal models for the study of breast cancer." (Office Action, page 5).

However, Applicant respectfully submits that the Examiner is taking the DMBA/rat results out of context, and is improperly ignoring the disclosures of Mückter as a whole, which teach away from the present invention. See *e.g. Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.* 796 F.2d 443, 230 U.S.P.Q 416 (Fed. Cir. 1986), *cert. denied*, 484 U.S. 823 (1987) (A single portion in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness, but rather, a reference should be considered as a whole, and portions teaching away from the claimed invention must be considered).

Specifically, the Examiner is ignoring that (1) in experiments on mice, thalidomide did not influence either the number or growth of tumors (pages 537-538); (2) the responses observed in the Sprague Dawley rats were only for a four to five week period (pages 533-535); (3) the responses observed in the Sprague Dawley rats abated after about six weeks of treatment, when tumors grew again at rates comparable with those of control (pages 536-537); and (4) the effect observed in Sprague Dawley rats is limited by the size of the tumor at the time of first administration and by the duration of treatment (pages 536-537). Thus, Applicant respectfully submits that the Examiner is failing to consider the reference as a whole. The Examiner must consider the art as a whole. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d at 1531 (Fed. Cir. 1988). Indeed, Mückter, when considered as a whole, actually teaches away from the present invention.

Even assuming, *arguendo*, that "one of ordinary skill would have given more weight to the guidance of the [Sprague Dawley] rat models," the Sprague Dawley rat models nonetheless discourage carrying out the present invention, because the anti-tumor effect abated after six weeks, and is limited by the size of the tumor at first administration and by the duration of treatment.

In sum, Mückter as a whole teaches away from the present invention and does not provide the legally required expectation of success. The three-part test for obviousness is not satisfied. Applicant respectfully submits that Mückter fails to render the present invention

obvious. For the foregoing reasons, Applicant respectfully requests that the obviousness rejection over Mückter be withdrawn.

3. Mau'ad fails to render the claimed invention obvious because the data presented in Mau'ad is preliminary and inconclusive.

The Examiner alleges that the present invention is unpatenable over Mau'ad because Mau'ad "teaches treatment of various types of cancer with thalidomide..." (Office Action, pages 5-6). Applicant respectfully disagrees.

Mau'ad tested the effects of the combinations of thalidomide, glucocorticoid, testosterone, dried thyroid, cell permeators and anabolics in cancer patients. (Our Regime on page 11 of the English translation). Mau'ad never used any agent alone (*Id.*), nor obtained any successful result from the single agent of thalidomide[2]. Clearly, Mau'ad would not provide one of ordinary skill in the art a reasonable expectation of success in the present invention.

Applicant respectfully points out that even the author acknowledged the preliminary and inconclusive nature of the data presented and further acknowledged that the dissemination of the publication was potentially premature. In the first sentence of the introduction, the authors state that "[i]t may appear, in the eyes of some, that our work requires greater maturation in order to warrant dissemination." Mau'ad, page 1, English translation. The author further acknowledges that their statistical analysis is "small in scope, short and reflective of human failings." Mau'ad, page 2, English translation. Moreover, the author further acknowledged that the data contain "relatively short observation time[s]" and that "supplementary examinations [were] insufficient at times." Mau'ad, page 31, English translation. The Examiner cannot ignore these quite relevant admissions of the author in determining obviousness. Applicant respectfully submits that Mau'ad fails to suggest the present invention because the data presented in Mau'ad is too preliminary and inconclusive.

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[2] Applicant submits that this is true even if, *arguendo*, as the examiner alleges, that claim 23 allows for additional elements/agents because of the phrase "comprising." (Office Action, pages 5-6). Mau'ad fails to render the use of thalidomide in the treatment of cancer obvious, regardless of whether additional agents are used in combination.

Further, none of the twenty-five patients in the study were treated with thalidomide for more than three months. (Mau'ad, pages 16-29, English translation). At least seven of these patients were only treated for one month – five of these patients were only treated for fifteen days or less. (Mau'ad, pages 24-29, English translation, Observations 16, 19-24). Further, Mau'ad discloses that five of these patients died after treatment, and the condition for at least three other patients worsened. (Mau'ad, pages 18-29, English translation, Observations 3-4, 8, 10, 13-14, 23-24).

Thus, Applicant submits that Mau'ad fails to suggest the claimed invention and would not provide to one of ordinary skill in the art that there would be a reasonable expectation of success in practicing the claimed methods. For these reasons, Applicant respectfully requests that the obviousness rejection over Mau'ad be withdrawn.

4. The Examiner fails to consider that the prior art as a whole teaches away from the present invention.

Further, Applicant respectfully submits that even assuming, *arguendo*, that Sugiura, Mückter, and Mau'ad suggest the present invention (Applicant maintains they do not), a *prima facie* case of obviousness has not been established, because the prior art as a whole teaches away from the present invention, and one of ordinary skill in the art would not find a reasonable expectation of success.

Applicant previously discussed twenty-two (22) references including Sugiura, Mückter, and Mau'ad in the response (pages 6-9) filed on October 31, 2005. A summary of these 22 references is submitted as Exhibit A for the Examiner's consideration. The office action is silent on nineteen (19) references except for Sugiura, Mückter, and Mau'ad. The Examiner "must not [consider] a reference in a vacuum, but against the background of the other references of record which may disprove theories and speculations in the reference..." *In re Ehrreich*, 590 F.2d 902, 908-909, 200 USPQ 504 (CCPA 1979). "The question in a § 103 case is what the references would *collectively* suggest to one of ordinary skill in the art." *Id.* (emphasis in original). See also *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391 (CCPA 1965) ("it is impermissible [with regard to § 103] *to pick and choose* from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary

to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." (emphasis added).

Applicant once again submits a summary of twenty-two (22) references as Exhibit A for the Examiner's consideration. As summarized in Exhibit A, the prior art as a whole teaches away from the present invention. Indeed, 19 references, not including Sugiura, Mückter, and Mau'ad, indicate that thalidomide was not successful in inhibiting tumors in animals and humans.

Moreover, Applicant respectfully points out that several references actually teach that thalidomide has cancer-promoting or carcinogenic activity. "[T]here can be little better evidence negating an expectation of success than actual reports of failure." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d. 1961 (Fed. Cir. 2003) (emphasis added). The references disclose not only failure but the complete opposite effect to the claimed invention.

In that regard, Applicant once again directs the Examiner's attention to Koch, *Progress in Medicinal Chemistry*, Vol. 22, 1985, pages 165-242, "Thalidomide and Congeners as Anti-inflammatory Agents." In particular, Koch discloses that articles exist that, contrary to the claimed invention, suggest that thalidomide has cancer-promoting or carcinogenic activity. The examiner must consider the references that teach away from the use of thalidomide in humans as claimed.

Highlights of other teachings away are discussed below and the full references are in the record for the Examiner's review. Miura *et al.* reported that thalidomide had a potentiating effect on methylcholanthrene oncogenesis. M. Miura, C.M. Southan and H. Wuest, *Experientia*, 26 (1970), page 305-306.

Roe and Mitchley tested thalidomide for potential carcinogenicity and found well-differentiated spindle cell sarcomas at the injection site in mice. F.J.C. Roe and B. C.V. Mitchley, *Nature*, December 7, 1963, volume 200, page 1016-17, "Thalidomide and Neoplasia."

Miller *et al.* reported that a 15-year-old patient with thalidomide-induced malformations developed a lymphoma of high malignancy. A. Miller, C.G. Scmidt, A. Horwitz and W. Kosenow, *Monatsschr. Kinderheilk*, 128 (1980) 27-29.

These three publications teach away from the claimed invention. Moreover, one skilled in the art reading the articles would also conclude that thalidomide does not provide a reasonable expectation of success for the treatment of tumors in humans.

Also, Koch cites several publications reporting on research on the anti-tumor activity of thalidomide and concludes, on the basis of these publications, that the anti-tumor activity of thalidomide remains doubtful. (Koch at 184). This conclusion itself is actual evidence of what the prior art would suggest to a person of ordinary skill in the art. For example, Koch discloses that Allegri treated twelve patients with various malignant tumors with thalidomide at doses from 50 mg to 1.05 g per day for periods of between 6 and 37 days, but there was no visible anti-tumor effect. Koch at 181; A. Allegri, *Gazz. Med. Ital.*, 123 (1964), 124-127. Thus, one skilled in the art would interpret that thalidomide would not be effective in inhibiting tumor formation or growth in humans as recited in the claimed invention.

Further, Woodyatt, *Lancet*, 1962, page 750, "Thalidomide" discloses that a woman having a malignant mixed mesodermal tumor of endometrium was treated with thalidomide but the tumor growth has not regressed, and that in fact there may have been a very slight increase in size. *Id.*

Traldi *et al.* reported that thalidomide was given to patients with malignant neoplastic diseases (gastric cancer, lymphoblastoma) and it had no influence on the neoplasm itself in all of these patients. A. Traldi, G.L. Vaccari and G. Davoli, *Cancro*, 18 (1965), 336-341.

Again, all of these studies failed to provide any promise for thalidomide as effective in inhibiting the formation or growth of tumors in humans. The studies neither provide with any suggestion, nor a reasonable expectation of success in inhibiting tumors in humans.

The reported inefficacy of thalidomide as an anti-tumor agent prior to the claimed invention had been reportedly confirmed in various animal experiments and in cell cultures. Juret *et al.* experimented an Ehrlich ascites tumor in the mouse and a solid epithelioma in the rat but could not find any suppressive activity of thalidomide. (Koch at 182; P. Juret *et al.*, *Seances Soc. Biol. Filial.*, 157 (1963), 246-249). Pagnini *et al.* studied the effect of thalidomide upon two experimental tumors, Ehrlich ascites carcinoma in the mouse and

myeloma in the rat, but no significant change in the mortality rates of the treated animals and the controls was found. (Koch at 180; G. Pagnini and R. Di Carlo, *Boll. Soc. Ital. Biol. Sperim.*, 39 (1963), 1360-63). Gaetani tested thalidomide to tumor-inoculated mice and found no influence of the drug upon development of various tumors such as Ehrlich ascites, myeloma, sarcoma and transplantable teratoma. (Koch at page 183; M. Gaetani, *Giorn. Ital. Chimioter.*, 11 (1964), 83-86).

In view of the articles teaching that thalidomide has cancer-promoting or carcinogenic activity, as well as the 19 other references suggesting thalidomide to be ineffective in inhibiting tumors, the prior art as a whole would not have provided one of ordinary skill in the art with any suggestion or a reasonable expectation of success in practicing the claimed methods in animals, much less in humans. Further, one of ordinary skill in the art would not have been motivated to combine or modify any references to arrive at the claimed invention.

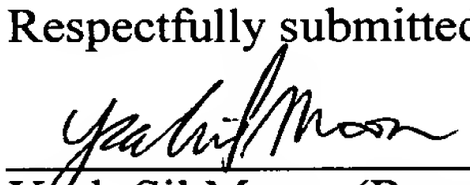
Therefore, Applicant respectfully submits that the prior art as a whole teaches away from the claimed invention, a *prima facie* case of obviousness has not been established, and respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

III. Conclusion

Applicant respectfully requests that the above amendments and remarks be entered in the file of this application. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Date: August 7, 2006

Respectfully submitted,



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Attachments

EXHIBIT A: SUMMARY OF REFERENCES

IDS #	Reference	Study	Result
C1	Sugiura et al., *GANN*, 1964, No. 55, pp. 57-60, "Effect of Thalidomide on Transplantable Mouse, Rat and Hamster Tumors"	*In Vivo* (Transplantable mouse, rat and hamster tumors)	18 ***No*** inhibition, 6 slight (sarcoma, Ehrlich carcinoma, Lewis lung carcinoma, Harding-Passey melanoma, Walker rat carcinosarcoma, Jensen rat sarcoma), and 1 moderate inhibition (Lewis bladder carcinoma)
C2	Mückter, *Antimicrobial Agents and Chemotherapy*, 1965, pp. 531-538, "Thalidomide and Tumors"	*In Vivo* (DMBA-induced tumors in rats, and spontaneously developing mammary carcinomas in mice)	***In***effective in mice, responded in rats for 4-5 weeks treatment but no response after 6 week
C3	Grabstald *et al.*, *Clinical Pharmacology and Therapeutics*, 1965, No. 6, pp. 298-302, "Clinical Experiences with Thalidomide in Patients with Cancer"	71 human patients with cancers of kidney, bladder, testes, prostate, gynecology, breast, digestive tract, parotid, lung, lymphoma, multiple myeloma, thyroid, gingiva and sarcomas	***In***effective except one renal cancer patient who had nephrectomy
C4	Joseph A. DiPaolo, *Cancer Chemotherapy Reports*, May 1963, No. 29, pp. 99-102, "Effect of Thalidomide on a Variety of Transplantable Tumors"	*In Vivo* (transplatable standard mouse and rat tumors; Ridgway osteogenic sarcoma and teratocarcinoma in mice, rhabdomyosarcoma in rats, and choriocarcinoma in hamsters)	***In***effective
C5	Joseph A. DiPaolo, *Proceedings of the Society for Experimental Biology & Medicine*, 1963, v114, pp. 384-387, "*In vitro* Test Systems for Cancer Chemotherapy, II. Correlation of *in vitro* Inhibition of Dehydrogenase and Growth with *in vivo* Inhibition of Ehrlich Asoites Tumor"	*In Vitro* and *In Vivo* (Ehrlich ascites tumor grown in mice)	***In***effective
C6	Joseph A. DiPaolo, *Science*, June 26, 1964, p. 1583, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells *in vitro*"	*In Vitro* (Ehrlich ascites tumor)	***In***effective
C7	A. Bach, *The Lancet*, June 8, 1963, No. 71, p. 1271, "Thalidomide in Cancer Chemotherapy"	*In Vivo* (mice with transplantable adenocarcinoma and stem-cell leukemia)	***In***effective
C8	A. Bach, *Acta Pathologica Et Microbiologica Scandinavica*, 1963 (59), pp. 491-499, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide"	*In Vivo* (transplantable mouse tumors)	***In***effective
C9	F. J. C. Roe and B. C. V. Mitchley, *Nature*, December 7, 1963, Volume 200, pp. 1016-17, "Thalidomide and Neoplasia"	*In Vivo* (sarcoma in mice)	***Carcinogenesis*** of sarcoma
C10	Chaundhry, *Cancer Research*, 1966, 26 part 1, 1884-86, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster"	*In Vivo* (fibrosarcoma in hamsters)	***In***effective
C11	Gershbein, *Cancer Letters*, 1991, 60:129-133, "The thalidomide analog, EM 12, Enhances 1,2-Dimethylhydrazine-Induction of Rat Colon Adenocarcinomas"	*In Vivo* (colon adenocarcinomas in rats)	***In***effective
C12	Olson *et al.*, *Clinical Pharmacology and Therapeutics*, 1965, 6(3):292-297, "Thalidomide (N-phthaloylglutamimide) in the treatment of advanced cancer"	21 human patients with 14 types of cancers (kidney, parotid, ovary, breast, melanoma, thyroid, lung,	***No*** objective evidence of tumor regression

IDS #	Reference	Study	Result
		multiple myeloma, chondrosarcoma, fibrosarcoma, reticulum cell sarcoma, mesenchymoma, liposarcoma, and rhabomyosarcoma)	
C13	MAU'AD MJ., Anais *Paulistas de Medicinae Cirurgia*, 1963, 86:13-40, "Clinical Improvements Obtained in Advanced Caner Patients with Treatment with Thalidomide Associated with Hormones"	22 malign and 3 benign tumor patients	Effective by combination, but *no test performed with thalidomide alone*
C14	Koch, *Progress in Medicinal Chemistry*, Vol. 22, 1985, pages 165-242, "Thalidomide and Congeners as Anti-inflammatory Agents"	Discussed various articles on tumor studies	Anti-tumor activity *doubtful*
C15	M. Miura, C.M. Southam and H. Wuest, Experientia, 26 (1970), 305-306	Mice	***Carcinogenesis*** of skin papillomas
C16	A. Miller, C.G. Schmidt, A. Horwitz and W. Kosenow, Monatsschr. Kinderheilk., 128 (1980) 27-29	Human patient	***Carcinogenesis*** of lymphoma
C17	A. Allegri, *Gazz. Med. Ital.*, 123 (1964), 124-127	Human patients (various malignant tumors)	***In***effective
C18	P. B. Woodyatt, *Lancet*, 1962, page 750, "Thalidomide"	Human patient (mesodermal tumor of endometrium)	***In***effective
C19	A. Traldi, G.L. Vaccari and G. Davoli, *Cancro*, 18 (1965), 336-341	Human patient (gastric cancer and lymphoblastoma)	***In***effective
C20	P. Juret *et al.*, *Seances Soc. Biol. Filial.*, 157 (1963), 246-249	Ehrlich ascites tumor in mouse and a solid epithelioma in rat	***In***effective
C21	G. Pagnini and R. Di Carlo, *Boll. Soc. Ital. Biol. Sperim.*, 39 (1963), 1360-63	Ehrlich ascites carcinoma in mouse and myeloma in rat	***In***effective
C22	M. Gaetani, *Giorn. Ital. Chimioter.*, 11 (1964), 83-86	Mice (Ehrlich ascites, myeloma, sarcoma and transplantable teratoma)	***In***effective